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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,472	10/04/2005	Masashi Ito	082368-001500US	8056

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

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10/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,472	ITO ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 17-19* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicant's response of May 16, 2008, to the non-final action dated December 31, 2007, has been entered. Claims 1-6, 8-9, 17 and 18 have been amended. No claims were cancelled or newly added.

Accordingly, claims 1-11 and 17-19 are pending in the application and under current examination.

Information Disclosure Statement

Document F1 submitted in compliance with 37 CFR §1.97(g),(h), and 37 CFR §1.98(a)(2) has been considered by the examiner and indicated as such on Supplemental Form SB/08.

Response to Claim Objections

Amended claims 2-5 were previously objected to due to minor informalities, in the previous office action dated December 31, 2007. In view of Applicants' claim amendments, the previous objection is hereby withdrawn.

New Claim Objection

Claim 6 is newly objected to for the following minor informalities. The claim recites "isolating adipocytes" in step 1, to establish "a primary culture of preadipocytes". The word "adipocytes" should be amended to "preadipocytes" for consistency.

Response to Claim Rejections - 35 USC § 112- New Matter

Claims 1-7, 9-11, 18 and 19 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, and introducing new matter, in the

previous office action dated December 31, 2007. Applicants have amended the claims to remove the new matter, thus obviating the ground for rejection. Accordingly, the previous rejection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 102

Claim 1-5, 8-9, 17 and 18 stand rejected under 35 U.S.C. 102(e) as being anticipated by Furcht et al. (U.S. Patent No. 7,015,037, Priority to Aug. 5, 1999). The rejection set forth on pp. 2-3 of the office action dated April 11, 2007, pp. 3-4 of the office action dated August 29, 2006, and pp. 5-7of the previous office action dated December 31, 2007 is maintained for reasons of record.

Applicants disagree with the rejection, and argue that the claims have been amended to set forth a population of primary cultured preadipocytes that stably maintain a foreign DNA encoding a protein that is secreted outside of a cell, and that Furcht does not disclose or suggest a population of preadipocytes or introducing a foreign gene into a preadipocyte cell. Instead, Furcht discloses differentiated, mature adipocytes derived from multipotent adult stem cells. Applicants' arguments have been fully considered, but are not found persuasive.

In response it is again noted that the instant specification defines the term adipocyte as, mature adipocyte and cells comprising the ability to differentiate into adipose tissue, such as preadipocytes…Preadipocytes normally exist as stromal cells that have not yet differentiated (pp. 4-5, bridging). There is no evidence that adipocytes established from adipose tissue are structurally or functionally different from those established from differentiated stromal mesenchymal stem cells. Moreover, the stromal cells described by Furcht et al. may be from an adult and derived from an organ, such as marrow (column 6, lines 16-19). Furcht et al. disclose multipotent adult stem cells (MASC) derived from bone marrow that can differentiate into bone marrow stromal cells and adipocytes (column 14, lines 31-37), thus meeting the limitation of preadipocytes. Thus, when given their broadest reasonable interpretation in view of the specification, the person of skill in the art would appreciate that the cultured population of preadipocytes claimed is not materially different from the cultured MASCs and stromal cells of Furcht et al., as both are obtained by differentiation and culture of pre-adipocytes.

With regard to the introduction of a foreign gene into a preadipocyte cell, Furcht et al. specifically describe a number of secreted genes that may be used for gene therapy of diabetes (column 30). Additionally described are viral transfer vectors, including retroviruses (column 32). Retroviral vectors are extensively described in column 35. The transduction of marrow derived stem cells with retroviral vectors encoding eGFP is described in Example 4 (column 48). Following *in vitro* culture and gene transfer, the transfected cells may be introduced locally or infused systemically (column 30). Specific examples of engraftment by intramuscular injection or stereotaxic transplantation into mice are described in Example 10 (columns 54-55). Furcht et al. further teach that the genetically altered stem cells can also be encapsulated in an inert carrier to allow the cells to be protected from the host immune system while producing the secreted protein (column 31). A number of pharmaceutically acceptable inert carriers materials, that include polymers and capsules are described in column 31. With specific reference to treatment for diabetes, the authors state that autologous stem cells that have been genetically altered with a retroviral vector to produce insulin at physiologically therapeutic levels can be encapsulated for delivery within the patient's tissues, to produce insulin for extended periods of time (column 31). Furcht et al. further describe stem cells transfected with factor IX, that secrete the protein for at least 8 weeks after infusion into mice (column 30).

Regarding ceiling culture, it is again noted that claim 18 is directed to a population of primary cultured preadipocytes, wherein the cells are obtained by ceiling culture. As such, the claim is directed to the product (i.e. the preadipocyte population), and not the process of making the product. Further, there is no evidence that adipocytes established from pre-adipocytes in adipose tissue are structurally or functionally different from pre-adipocytes established from differentiated stromal mesenchymal stem cells, especially given the instant specification's definition of an adipocyte (see above). As stated in MPEP 2113: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Thus, the rejection is maintained for reasons of record and the preceding discussion.

Response to Claim Rejections - 35 USC § 103

Claims 9-11 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Furcht et al. (U.S. Patent No. 7,015,037, Provisional Priority to Aug. 5, 1999), in view of Crystal et al. (U.S. Patent Publication No: 2002/0076395; filed Dec., 23, 1998), and further in view of Baetge et al. (U.S. Patent No: 5.639.275; filed May 25, 1995). The rejection set forth on pp. 3-4 of the office action dated April 11, 2007, pp. 5-6 of the action dated August 29, 2006, and pp. 8-9 of the previous office action dated December 31, 2007, is maintained for reasons of record.

Applicants traverse the rejection, arguing that the combined disclosures of the cited references do not disclose or suggest each and every element of the claimed invention, because Furcht fails to teach or suggest primary cultured preadipocytes or preadipocytes that stably maintain a foreign DNA encoding a protein that is secreted outside of a cell. Applicants further argue that the population of primary cultured preadipocytes and the implant composition of the present invention comprising a population of primary cultured preadipocytes, possess advantageous effects compared to compositions comprising mature adipocytes. Specifically, the mature adipocytes disclosed by Furcht, which are differentiated from stem cells, and the mature adipocytes comprised in the implant composition of Crystal do not proliferate. Applicants' arguments have been fully considered, but are not found persuasive.

In response, Applicants are directed to the response provided above regarding the teachings of Furcht et al., their MASCs and stromal cells, and their genetically altered derivatives. Furcht et al. describe transduction of marrow derived stem cells with retroviral vectors carrying a gene of interest (as described above), and further describe autologous stem cells that have been genetically altered with a retroviral vector to produce insulin at physiologically therapeutic levels can be encapsulated for delivery within the patient's tissues, to produce insulin for extended periods of time (column 31). Thus, the implantation of stem cells or preadipocytes is specifically taught by Furcht et al., and is not limited to mature adipocytes.

Regarding Applicants' argument against the reference of Crystal individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Thus, the rejection of claims 9-11 is maintained for reasons of record and the preceding commentary.

Claims 6-7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Furcht et al. (U.S. Patent No. 7,015,037, Provisional Priority to Aug. 5, 1999), in view of Hertzel et al. (J. Lipid Res. 41:1082-1086; 2000). The rejection set forth on pp. 4-5 of the office action dated April 11, 2007, and p. 9 of the previous dated December 31, 2007, is maintained for reasons of record.

Applicants traverse the rejection, arguing that Furcht does not disclose or suggest a population of preadipocytes or introducing a foreign gene into a preadipocyte cell. Applicants further argue that the differentiated, primary adipocytes described in Hertzel are distinguishable from preadipocytes, as Hertzel recovered "the floating adipocytes," and thus would not be able to isolate preadipocytes, which are heavier than mature adipocytes and should precipitate when subjected to centrifugation and, Hertzel's primary adipocytes shown in Figures 1 and 2 are all round-shaped, and none of the cells has fibroblast-like morphology. Applicants' arguments have been fully considered, but are not found persuasive.

With regards to the teachings of Furcht et al. relating to preadipocytes, Applicants are directed to the response provided above. As Furcht et al. provide a disclosure for preadipocytes, such teachings are not required by the secondary reference of Hertzel et al. was provided to address the issue of establishing a primary culture of adipocytes from adipose tissue. Hertzel et al. describe the primary culture of adipocytes from gonadal fat pads (first column, p. 1082) and their transduction with adenoviral vector encoding foreign DNA (Abstract). Hertzel et al. additionally describe the enrichment of the primary culture of adipocytes by repeated washes and centrifugation, followed by recovery of floating adipocytes (first column, p. 1082). Applicants' are directed to page 11 of their own specification, teaching the isolation of primary cultured adipocytes by separating the floating layer following centrifugation, and subjecting it to ceiling

culture, wherein after 10-14 days, the cells adhere to the ceiling surface (lines 12-19). Thus, for ceiling culture, the cells must necessarily float up to the ceiling.

Thus, the rejection of claims 6-7 is maintained for reasons of record and the preceding discussion.

Response to Claim Rejections - 35 USC § 103

Claims 6 and 19 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Furcht et al. (U.S. Patent No. 7,015,037, Provisional Priority to Aug. 5, 1999), in view of Hertzel et al. (J. Lipid Res. 41:1082-1086; 2000), and further in view of Zhang et al. (J. Endocrinology 164:119-128; 2000). The rejection set forth on pp. 10-12 of the previous dated December 31, 2007, is maintained for reasons of record.

Applicants disagree with the rejection, arguing that neither Furcht nor Hertzel disclose or suggest any methods of producing populations of primary cultured preadipocytes, and Zhang does not supply the elements missing from Furcht and Hertzel.

Applicants' arguments have been fully considered, but are not found persuasive. Applicants' arguments with regards to the teachings of Furcht et al. and Hertzel et al. were addressed in the commentary provided above.

The reference of Zhang et al. was provided to describe the ceiling culture of adipocytes and preadipocytes that uses their buoyant properties to allow them to adhere to a floating glass surface.

Thus, the rejection of claims 6 and 19 is maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 1-11 and 17-19 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE**

FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1633

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